SL65.0155, a 5-HT4 PARTIAL AGONIST REVERSES MEMORY DEFICITS INDUCED BY β25-35 AMYLOID PEPTIDE I.C.V. ADMINISTRATION IN MICE

Alexandre URANI, Olivier BERGIS, Guy GRIEBEL

Introduction

Alzheimer’s disease (AD) is a neurodegenerative disorder characterized notably by cognitive decline.

5-HT receptor agonists have been shown recently to improve learning and memory in rodents and, as such, represent potential drug candidates for the symptomatic treatment of AD. SL65.0155, a 5-HT4 receptor partial agonist (S-GSKNKGAIIGLM) that is necessary and sufficient to induce neuronal toxicity, in mice. It is an important model of 5-HT4-mediated toxicity.

The aim of these studies was to assess the effects of SL65.0155 on the cognitive deficits induced by i.c.v. infusion of β25-35 in different memory models in mice.

Methods

Animals

C57Bl/6 or CD1 male mice weighing 28±2 g at the time of testing were used. They were fed ad libitum and kept in a controlled environment (12h/12h dark/light cycle, 21°C, 60% humidity).

β25-35 amyloid peptide i.c.v. administration

β25-35 amyloid peptide fragment contains the 11 amino-acid (S-GSKNKGAIIGLM) that are necessary and sufficient to produce memory deficits (Moser et al. 2002, JPET 302, 731-41).

Mice were used for behavioural experiments 10 days after injection. Control mice were injected with the same dose of the scrambled peptide (same amino acids but in a random order).

Y-maze

The maze was made of 3 identical arms at equal angles. When mice are allowed to freely explore the maze, spontaneous alternation behaviour consists in visiting the 3 different arms alternatively.

Object Recognition task

The object recognition test takes place in a square open field (52 cm) and consists in 3 sessions. Mice are firstly habituated to the context for 2 min at 24h prior to acquisition. For the acquisition, mice are placed in the context in the presence of 2 identical objects. Animals are exposed to the novel object for 2 min and then explore it for 3 min. After the 3 min testing period, mice are placed again in the enclosure containing one of the previous object and a new one. If the novel object is the one remembered, mice first explore the object and spend the same time exploring the two objects.

Conclusion

SL65.0155, a 5-HT4 receptor partial agonist displayed pre-cognitive activity in two types of memory using a pathophysiological model of Alzheimer’s disease in mice.

SL65.0155 facilitated episodic memory in the object recognition task in normal mice.

SL65.0155 reversed the working memory and episodic memory deficits induced by β25-35 peptide i.c.v. administration in mice.

These effects were fully blocked by GR113808, a 5-HT4 antagonist, confirming the involvement of the 5-HT4 receptor in the pre-cognitive activity of SL65.0155.

Taken together, these results strengthen further the involvement of the 5-HT4 receptor in learning and memory and confirm the potential of SL65.0155 as a symptomatic treatment of the cognitive deficits linked to Alzheimer’s disease.